## REMARKS

Claims 2-14 and 17 are pending in the instant application. Claims 1, 15-16 are cancelled without prejudice or disclaimer. Claims 5, 8, 11, and 12 are withdrawn without prejudice or disclaimer. Claims 14 and 17 have been amended. Following entry of the amendment, claims 2-4, 6-7, 9-11, 13-14, and 17 are pending.

Support for the amendment of claims 14 and 17 can be found at least, for example, in the originally filed specification at page 5, lines 5-10; at page 4, lines 14-17; and at page 3, lines 9-21; and in the originally filed claims. No new matter is added by way of these amendments.

Amendment and cancellation of the claims here are not to be construed as an acquiescence to any of the rejections/objections made in the instant Office Action or in any previous Office Action, and were done solely to expedite prosecution of the application. Applicants hereby reserve the right to pursue the claims as originally filed, or substantially similar claims in one or more subsequent patent applications.

### Claim Rejections – 35 U.S.C. § 112, first paragraph

The Office Action states that claim 14 is rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement. Applicants respectfully disagree and traverse the rejection.

The Office acknowledges that Applicants have enabled methods for treating psoriasis using specific embodiments of formula (I) in particular animals. However, the Office states that Applicants have not enabled the full scope of the claim, i.e., have not enabled the treatment of psoriasis using the genus of embodiments represented by formula (I). Without acquiescing to any of the rejections and in order to expedite the prosecution of this case, Applicants have amended claim 14 to recite that "R is a $C_{16-24}$ unsaturated hydrocarbon group interrupted β to the carbonyl group by a heteroatom or group of heteroatoms selected from S, O, N, SO, $SO_2$;... and X is $CF_3$."

Claim 14, as currently amended, specifies the nature of the electron withdrawing group, specifies the presence of a heteroatom, specifies the heteroatom to be present ß to the carbonyl, and specifies a limited unsaturated hydrocarbon group. Responding to the allegation that docoahexaneoic acid (DHA) is encompassed by formula (I), Applicants note that the amended claim does not read on DHA, thus traversing the basis for this rejection. Regarding the

rejection of claim 14 for reciting "X is an electron withdrawing group," Applicants have specified that "X is $CF_3$," thereby rendering moot the basis for this particular rejection. Therefore, the breadth of claim 14 is reduced relative to that of previously presented claim 14.

The genus presently recited by claim 14 is well within the scope of enablement provided by the specification, at least for the reasons previously presented in Applicants' Response dated February 25, 2008 (in reply to the Office Action of September 25, 2007). At page 4, the Office Action alleges that the specification lacks a sufficient number of examples necessary to represent the variation present in Formula (I). In continuation of the arguments previously presented, Applicants submit that the specification provides working examples showing that at least two compounds belonging to the claimed genus are effective for the treatment of psoriasis and clearly describes methods of using compounds of formula I for the treatment of psoriasis. Specifically, Applicants have discovered that compounds of formula I selectively inhibit a specific subtype of $PLA_2$, IVa $PLA_2$, and that such compounds are particularly potent in inhibiting eicosanoid production, thereby reducing inflammation and treating psoriasis (page 1, lines 21-36, page 3, lines 1-8).

Applicants have disclosed various compounds in the Examples, two of which, AKH217 and $EPASCOCF_3$, are representative of the class of compounds that fall within the scope of claim 14, as currently amended. These compounds, whose structures are shown at page 9, lines 15-34, selectively inhibit IVa PLA2 (page 12, lines 1-3) and are useful in treating inflammation, hyperproliferation, and cell activation that are related to eicosanoid production in psoriatic skin. In particular, $EPASCOCF_3$ and AKH217 inhibit IVa PLA2 as shown in Figures 1 and 2 (page 6, lines 22-35). In kinetic studies, $EPASCOCF_3$ and AKH217 all inhibited PLA2 activity with similar potency (page 12, lines 27-30). In fact, $EPASCOCF_3$ had an $IC_{50}$ value of 3.5 μM, while the commercially available PLA2 inhibitor AACOCF3 had an $IC_{50}$ value of 5.8 μM. Moreover, Applicants discovered that AKH217 inhibited NF-κß activation by 91% in human skin cells stimulated with the proinflammatory cytokines IL-1 or TNFα

In sum, Applicants have clearly shown that compounds encompassed by claim 14 selectively inhibit IVa PLA2 and are useful for the treatment of psoriasis. In view of this disclosure, one of skill in the art would expect that other compounds that share the structural features defined by formula (I) would also have similar activities. Therefore, Applicants respectfully submit that that exemplification of these compounds is at least sufficient to support

the breadth of claim 14. Indeed, the instant Office Action at page 3 expressly states that the specification as filed is "enabling for treating psoriasis in certain animals by administration of specific embodiments of formula (I)." In the absence of reasoning that establishes why a person skilled in the art could not use the genus as a whole without undue experimentation, the enablement rejection of claim 14 under 35 U.S.C. § 112, first paragraph, should be withdrawn.

Furthermore, the Office Action states that claims 2-4, and 6-13 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. Applicants have withdrawn claims 5, 8, 11, and 12 without prejudice or disclaimer, thereby rendering the rejection moot as to those claims. The remaining Claims 2-4, 6-7, 9-10, and 13 all depend from claim 14, and therefore incorporate the elements of claim 14. Specifically, Claims 2-4, 6-7, 9-11, and 13 also include the elements that "R is a $C_{16-24}$ unsaturated hydrocarbon group interrupted β to the carbonyl group by a heteroatom or group of heteroatoms selected from S, O, N, SO, $SO_2$;... and X is $CF_3$." Once again, Applicants respectfully disagree and traverse the rejection.

In support of the rejection of claims 2-4, and 6-13 under 35 U.S.C. §112, first paragraph, Office Action (at pages 9 and 10) cited (1.) the nature of the invention, state and predictability of the art, relative skill level, and (2.) breadth of the claims as reasons for the rejection. However, claim 14, as currently amended, specifies the the electron withdrawing group as $CF_3$, specifies the presence of a heteroatom (S, O, N, SO, $SO_2$), specifies the heteroatom to be present ß to the carbonyl, and specifies a limited unsaturated hydrocarbon group. Once again, docosahexaneoic acid (DHA) no longer reads on any of claims 2-4 and 6-13, and the rejection is rendered moot. Furthermore, for reasons described above regarding claim 14, claims 2-4 and 6-13 are commensurate with Applicants's disclosure, which demonstrates in the Examples that compounds encompassed by base claim 14 selectively inhibit IVa PLA2 and are useful for the treatment of psoriasis

In support of the enablement rejection, the Office Action (at page 11) cited (3.) the amount of direction or guidance provided and the presence or absence of working exmaples, alleging that the amount of direction or guidance is insufficient and the number of working examples is inadequate. As M.P.E.P. §2164.02 states: "The presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, even though it is a factor to be considered along with all the other factors." Nevertheless, Applicants have disclosed various compounds in the Examples at least two of

which, AKH217 and EPASCOCF$_3$, are within the scope of the claims, as presently amended. The two species, which have been adequately characterized in the Examples, are representative of the entire genus described by Formula (I). Thus, it would be apparent to one of skill in the art that the compounds described by Formula (I) would be effective selective IVa PLA2 inhibitors and useful for treating psoriasis.

Additionally, Applicants have shown that a compound described by Formula (I) has utility in the inhibition of enzymes associated with psoriasis and that it would be apparent to one skilled in the art how to treat psoriasis using the compound. Applicants have clearly taught one how to treat psoriasis using the compounds of the invention. The standard set forth for enablement in 35 U.S.C. 112, first paragraph, requires that Applicants provide a description of the invention sufficient "to enable any person skilled in the art to which it pertains...to make and use" the invention. The specification describes how to synthesize the compounds of the invention in the paragraphs at page 5, lines 14-31; and how to make medicaments comprising the compounds of the invention at the section spanning page 5, line 32 - page 6, line 5. The specification describes how to use them in the section at page 6, lines 5-18. In particular, the specification teaches that the compound can be formulated as a topical composition for application to the skin (page 6, lines 8-10).

The Office Action (at page 12) also cited (4.) the quantity of experimentation necessary in support of the enablement rejection. In view of the preceding arguments regarding item 1-3 of the Office Action, the claims are consistent with the scope of what is disclosed and would convey to one of skill in the art "how to make and use" the invention. The claims are enabled from the examples in the specification correlating *in vitro* utility and *in vivo* activity. Regarding the Office's stance on enablement when such a correlation is relied upon, M.P.E.P. §2164.02 is clear that "a rigorous or an invariable exact correlation is not required," citing *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):

> [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and **therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence**. (Citations omitted.) [Emphasis added]

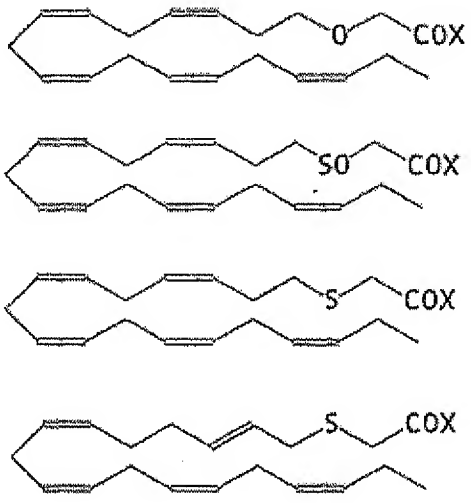
Because claim 14 has been amended to recite fewer elements than before, Applicants submit that the claim 14, and the claims depending therefrom, do not therefore cover many different types of compounds. Both the nature of the X group and the position of the heteroatom are limited to a single group (i.e., $CF_3$) or position (i.e., β to the carbonyl group), respectively. Applicants allow for five different heteroatoms and the hydrocarbon group must have at leave five double bonds which are non-conjugated and must have between 16 and 24 carbon atoms. Thus, there are only a few ways of fitting five non-conjugated double bonds into a $C_{16-24}$ hydrocarbon group. The compounds exemplified in the specification are representative of the compounds being presently claimed and undue experimentation would not be required to practice the methods of the invention using the presently claimed compounds. The claims are at least commensurate with what is taught by the specification.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 14, 2-4, 2-4, 6-7, 9-10, and 13 under 35 U.S.C. §112, first paragraph.

**Claim Rejections – 35 U.S.C. § 112, second paragraph**

The Office Action states that claim 10 is rejected under 35 U.S.C. §112, second paragraph as failing to set forth the subject matter which Applicants regard as their invention. Applicants respectfully disagree and traverse the rejection.

The Office Action at page 12 states that "It is unclear how [the compound ] could be an embodiment of formula (I)." However, Claim 10 has been amended to recite "wherein the RCOX group is




"

Thus, the present amendment renders the rejection against claim 10 moot.

**Claim Rejections – 35 U.S.C. § 102**

Claims 2-4, 5-11, 14, and 17 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Miller et al., "Dietary Supplementation with Ethyl Ester Concentrations of Fish Oil (n-3) and Borage Oil (n-6) Polyunsaturated Fatty Acids Induces Epidermal Generation of Local Putative Anti-Inflammatory Metabolites," Journal of Investigative Dermatology, 1991, 96(1), 98-103 ("Miller"). Additionally, Claims 2-4, 5-11, 14, and 17 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by JP11-199493 ("the JP '493 application"). Applicants respectfully disagree and traverse the rejections.

In order to anticipate the invention as claimed, the cited referenced must teach each and every element of the claim. However, without in any way acquiescing to the rejections, Applicants have amended the claims to recite "X is $CF_3$." Neither of the cited references describes a compound comprising a $CF_3$ group. Thus, the presently amended claims do not include the acids and esters mentioned in the cited references, thereby rendering the rejection moot as to those claims. Applicants have also withdrawn claims 5, 8, 11, and 12 without prejudice or disclaimer, thereby rendering the rejection moot as to those claims.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 2-4, 6-7, 9-10, 14 and 17 under 35 U.S.C. §102(b) over Miller or the JP '493 application.

**Declaration under 37 C.F.R. § 1.132**

Applicants file concurrently herewith the Declaration of George Kokotos, Ph.D., pursuant to 37 C.F.R. § 1.132 (the "Declaration") for the Examiner's consideration. The Declaration represents an opinion from a qualified expert who is a respected organic chemist. Professor Kokotos has considered the cited references and has concluded that the teachings in the cited references would not have taught or suggested one of skill in the art that the inhibitors could be used for the treatment of psoriasis.

**Claim Rejections – 35 U.S.C. § 103**

Claim 14 is rejected under 35 U.S.C. §103(a) as allegedly obvious over Johansen et al., *Prog Surg*. 1997 24: 225-231 ("Johansen") in view of Holmeide et al., *J. Chem. Soc., Perkin Trans*. 2000 1: 2271-2276 ("Holmeide"). Additionally, Claims 2-4, 6-13 and 17 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Johansen in view of Holmeide. In accordance with Applicants' obligation under 37 C.F.R. §1.56, Applicants state that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made. Responding to the Examiner's allegation that Claims 2-4, 6-14, and 17 are obvious in view of the references cited, Applicants respectfully disagree with the rejection and request that it be withdrawn. Applicants also submit concurrently herewith a Declaration from an expert, i.e., Professor George Kokotos, to overcome the rejections.

In order to make out a *prima facie* showing of obviousness, the Examiner must establish that there is some motivation in one or the other of the cited references or in the state of the art at the time the invention was made to combine the references, the combination of references must teach or suggest each and every element of the claimed invention, and there must be some reasonable expectation of success in making and using the invention.

The Office Action rejects independent claim 14 and claims 2-4 and 6-13 depending therefrom, as allegedly obvious over the cited references. Applicants have withdrawn claims 5, 8, 11, and 12 without prejudice or disclaimer, thereby rendering the rejection moot as to those claims. Without in any way acquiescing to the rejection and in order to expedite the prosecution of this case, Applicants have amended claim 14 to recite that "R is a $C_{16-24}$ unsaturated hydrocarbon group interrupted β to the carbonyl group by a heteroatom or group of heteroatoms selected from S, O, N, SO, $SO_2$;... and X is $CF_3$." Because Claims 2-4, 6-7, 9-10, and 13 from claim 14, claims 2-4, 6-7, 9-10, and 13 also incorporate the elements of claim 14.

Applicants respectfully submit that Johansen and Holmeide do not provide the requisiste motivation or guidance to combine the two references in the manner suggested by the Office Action. Johansen merely describes a correlation between levels of type II $PLA_2$, termed $npPLA_2$ (page 226, 4th and 5th paragraph), and psoriasis. Specifically, Johansen did not link psoriasis to IVa $PLA_2$. Moreover, Johansen did not detect any correlation between levels of $cPLA_2$ (page 228, 3rd full paragraph), of which IVa $PLA_2$ is a subtype. Nevertheless, Johansen states, in conclusion, that

> Altogether, ***selective inhibitors for $PLA_2$ enzymes*** should have a potential in curing some of the inflammatory symptoms, including epidermal hyperproliferation due to increased leukotriene production, related to eicosanoid production and cell activation in both epidermis and dermis in psoriasis. [page 230, last paragraph; emphasis added]

Absent any data to support Johansen's hypothesis, this conclusory statement is a broad generalization that fails to represent the complexity of disease pathology and in particular the complexity of the $PLA_2$ family of enzymes, as stated in the Declaration at paragraph 13. Johansen is silent regarding any correlation between levels of $cPLA_2$ and psoriasis. Thus, one skilled in the art would not be motivated to inhibit $cPLA_2$ based on Johansen.

The Office has further cited Holmeide as an alleged remedy for this deficiency of Johansen. Applicants respectfully disagree. As stated in the Declaration at paragraph 7, Holmeide merely describes the synthesis of polyunsaturated trifluoromethyl ketone (Compound 18). Holmeide fails to teach that Compound 18 is a ***selective inhibitor*** of $cPLA_2$. Contrary to the Examiner's assertion, Holmeide does not teach the utility of Compound 18 as a selective inhibitor. In conclusion, Holmeide states that, *inter alia*, Compound 18 has been prepared as a **potential** inhibitor of the enzyme cPLA2. Although **preliminary** testing indicated that Compound 18 acted as an inhibitor, the test results were apparently too preliminary to be published by Holmeide. Moreover, Holmeide failed to present any test protocols or the analysis of any actual results, as stated in the Declaration at paragraph 8. Holmeide may teach Compound 18 as a *potential* $cPLA_2$ inhibitor, but there is nothing in Holmeide to imply that Compound 18 or any other compound described therein selectively or preferentially inhibits $cPLA_2$. For this reason alone, there is no motivation to combine the references in the manner suggested in the Office Action.

The Office has also argued that the enzyme differences are immaterial to the nature of the rejection as Johansen mentions that selective $PLA_2$ inhibitors have a potential in curing psoriasis. Applicants respectfully disagree. It is important to remember that $PLA_2$ enzymes are ubiquitously expressed, as is known in the art. As stated in the Declaration at paragraph 16, the $PLA_2$ family of enzymes is grouped into three major groups secretory (s), cytosolic (c), and cytosolic calcium independent (i) $PLA_2$. Furthermore, $cPLA_2$ is divided into 12 groups, within which group IV $PLA_2$ is still further subdivided into groups IVa, b, c, d, e and f. Regulatory important structures in group IVa $PLA_2$ are the C2 domain and the catalytic domain. Group IVb

$PLA_2$ shares only 30% homology with group IVa within the same domains, and with group IVd only 29% (although 50 % homology to group IVb). Group IVd releases linoleate preferably over arachidonate. $PLA_2$ enzymes group IVe and f also share higher homology with group IVb than IVa. The $cPLA_2$ group IVc has many structurally and functionally differences compared to group IVa, it lacks phosphorylation sites and the C2 domain, and its mRNA is not ubiquitous like the group IVa mRNA, all indicating fundamental differences in its regulation compared to group IVa $PLA_2$ (reviewed in Ghosh et al., 2006). The compounds of the invention target specifically the group IVa $PLA_2$ compared to b-f, by utilizing its arachidonate selectivity and its active site geometry.

Neither Johansen nor Holmeide appreciated these aspects of $PLA_2$ inhibitors. At most, from a plain reading of Johansen, for psoriasis treatment more than one subtype of a $PLA_2$ isoenzyme would need to be inhibited (page 226, 2nd paragraph). In contrast, Applicants have further characterized the molecular pathology of psoriasis and identified a particular enzyme within the $cPLA_2$ family, i.e., IVa $PLA_2$, that can be inhibited to treat psoriasis. As stated in the Declaration at paragraph 18, Johansen does not suggest the inhibition of $cPLA_2$ for the treatment of psoriasis, let alone consider which among the $cPLA_2$ enzyme subtypes should be inhibited. In this regard, Johansen does not teach any potentially relevant compounds which might be useful, other than arachidonic acid (AA) or a simple hydroxy analogue thereof, as stated in the Declaration at paragraph 20.

Regardless, if there is any teaching of a selective inhibitor in Johansen for the treatment of psoriasis, it is for the inhibition of $npPLA_2$, which is the $PLA_2$ enzyme Johansen characterizes as overexpressed in psoriasis, as stated in the Declaration at paragraph 19. One would not be motivated to inhibit $cPLA_2$ levels which were "similar ... in normal compared to psoriatic skin" (page 230, 3rd full paragraph). It would not be obvious to make that selection at all. Rather it would be inventive over Johansen to realize that the way to treat psoriasis would be to inhibit the enzyme which is not over expressed in normal skin, as Applicants have taught. There are a large number of phospholipid enzymes which control a wide variety of intracellular functions and it is surprising that the claimed compounds are specific for a particular enzyme within the phospholipase A2 group.

Nor does Holmeide supply any teaching or motivation to remedy this deficiency of Johansen. Holmeide mentions various symptoms with which $cPLA_2$ enzyme can be associated

(see, e.g., page 2271, 1st paragraph of the Introduction). As stated in the Declaration at paragraphs 8 and 9, Holmeide teaches $cPLA_2$ generically, and discusses inhibition thereof in the context of pain, inflammation, allergy, and blood platelet aggregation, which are symptoms of countless thousands of diseases and Holmeide fails to identify any specific conditions. In particular, psoriasis is not mentioned. Holmeide arguably teaches that some of the compounds it discloses might have potential in the treatment of a huge variety of diseases, but it fails to identify any particular conditions which could be treated. Holmeide does not specifically teach that $cPLA_2$, let alone IVa $PLA_2$, can be selectively inhibited to treat psoriasis.

Nor is there any teaching in the art that would supply the motivation to use any inhibitor of $PLA_2$ to treat any disease, in order to combine Johansen with Holmeide in the manner suggested by the Examiner. Even assuming there were, for the sake of argument, it would not be obvious that simply because a group of compounds inhibit one $PLA_2$ subtype would they inherently inhibit all subtypes across the group. As stated in the Declaration at paragraphs 11 and 17, each of the enzyme subtypes of group IV have independent structures and would require inhibitors which are subtype specific, i.e., each individual $cPLA_2$ enzyme requires a specific inhibitor for selective inhibition. Rather, to one of skill in the art, a specific inhibitor of a target $PLA_2$ enzyme would be required to treat a disease successfully. As stated in the Declaration at paragraph 15, 12-epi-scalaradial is a potent inhibitor of $sPLA_2$, but shows much lower inhibition of $cPLA_2$ activity (Thwin et al., 2003). BEL, a potent inhibitor of $iPLA_2$ present in the heart, and the macrophage-like cell line P338D (Balsinde and Dennis, 1997), is a 1000-fold more potent and selective inhibitor for $iPLA_2$ than for group IVa $PLA_2$. Clearly, therefore, compounds can target specific $PLA_2$ enzymes, but neither of the cited references teaches a compound of the invention as a specific inhibitor of IVa $PLA_2$ or links the enzyme IVa $PLA_2$ to psoriasis.

Applicants further submit that Holmeide instead teaches the broad inhibition of $cPLA_2$ enzymes, absent a specific teaching regarding $cPLA_2$ subtypes. In contrast, the originally filed specification teaches that inhibition of many subtypes is undesirable as it will lead to side effects (page 2, lines 21-32). Thus, Applicants' invention is based, in part, on the surprising discovery that compounds of formula I selectively inhibit a specific subtype of $PLA_2$, IVa $PLA_2$, and that such compounds are particularly potent in inhibiting eicosanoid production, thereby reducing inflammation and treating psoriasis (page 1, lines 21-36, page 3, lines 1-8). As stated

in the Declaration at paragraphs 10, 11 and 17, the compounds of the invention are specific for IVa $PLA_2$ and will thus potentially have fewer side effects than an inhibitor of a number of $PLA_2$ enzymes.

Thus, there is nothing in either of the cited references or in the state of the art at the time the invention was made that provides one of ordinary skill in the art with motivation to combine the references in the manner proffered by the Examiner. Specifically, Johansen teaches selective inhibitors for treating psoriasis, but does not teach the compounds. Holmeide teaches compounds, but does not teach them as selective inhibitors of Johansen or useful for the treatment of psoriasis. Without the requisite motivation or guidance to combine the cited references, their combination does not put one of ordinary skill in the art in possession of the claimed invention, as stated in the Declaration at paragraphs 21. Therefore one of ordinary skill in the art would not have a reasonable expectation of success in making and using the claimed invention based on these references.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 14, 2-4, 6-7, 9-10, and 13 under 35 U.S.C. §103(a).

Without acquiescing to any of the rejections and in order to expedite the prosecution of this case, Applicants have amended 17 to recite "thereby selectively inhibiting the enzyme IVa $PLA_2$." Thus, the present invention includes inhibiting the enzyme IVa $PLA_2$.

In contrast, Johansen fails to teach or suggest inhibiting a $cPLA_2$ subtype enzyme, let alone IVa $PLA_2$. Instead, Johansen teaches inhibiting either $npPLA_2$ or $cPLA_2$. As in Johansen, one could make a general statement that any inflammatory condition can be treated by a $PLA_2$ inhibitor. However, this is a dramatic oversimplification, as stated in the Declaration at paragraphs 13 and 14. Currently, there are 15 groups and many subgroups of $PLA_2$ enzymes. Probative evidence is required to establish if a $PLA_2$ group and subgroup is the therapeutic target for a particular inflammatory disease. Although Johansen describes inhibiting $PLA_2$, Johansen neither teaches nor suggests inhibiting IVa $PLA_2$ in particular.

As acknowledged in a previous Office Action of September 25, 2008, Johansen fails to teach or suggest the use of compounds of formula (I) for the treatment of psoriasis (Office action, page 9, first paragraph). The Examiner has further cited Holmeide as an alleged remedy for this deficiency of Johansen.

However, the claims as currently amended recite "thereby selectively inhibiting the enzyme IVa $PLA_2$." As indicated above, Johansen does not teach or suggest inhibiting IVa $PLA_2$. Likewise, Holmeide also does not teach or suggest inhibiting IVa $PLA_2$ and, therefore, does not make up for the deficiencies in Johansen. Thus, neither of the cited references, either alone or in combination, identifies any of the compounds of the invention as a specific inhibitor of IVa $PLA_2$.

Furthermore, neither of the cited references specifically links IVa $PLA_2$ to psoriasis, as Applicants have shown. Holmeide mentions various diseases with which $cPLA_2$ can be associated. However, $cPLA_2$ is an ubiquitous enzyme. It would not be apparent to one skilled in the art to use any inhibitor of $cPLA_2$ for the treatment of any disease because a specific inhibitor of the target enzyme would be required, as stated in the Declaration at paragraph 17.

There is nothing in either of the cited references or in the state of the art at the time the invention was made that provides one of ordinary skill in the art with motivation to combine the references in the manner proffered by the Examiner. Assuming for the sake of argument that there were such motivation, the combination does not teach or suggest each and every element of the claimed invention because neither reference teaches or suggests inhibiting IVa $PLA_2$.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of Claim 17 under 35 U.S.C. §103(a).

The Office comments that Applicants have not offered comparative data relative to Johansen. Johnasen is essentially an article characterizing $PLA_2$ in psoriasis, so there are no results in this paper equivalent to those of the inventors with which to compare. There is no attempt in Johansen to inhibit any enzyme or to characterize the inhibition of $PLA_2$. Rather, the results are directed to examining which $PLA_2$ enzymes are overexpressed in psoriatic skin. Regarding the scope of the data Applicants submitted in the previous Response of February 25, 2008, the scope of what the data show is discussed in the above section addressing the rejections under 35 U.S.C. §112.

## CONCLUSION

In view of the foregoing arguments, Applicants respectfully request reconsideration and withdrawal of all pending objections/rejections and allowance of the application with Claims 2-4, 6-7, 9-11, 13-14, and 17 presented herein. If a telephone call with Applicants' representative would be helpful in expediting prosecution of the application, Applicants invite the Examiner to contact the undersigned at the telephone number shown below.

Applicants believe that no fee is due to consider the present response. Nevertheless, the Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. **04-1105**, under Order No. 64490(53385).

Dated: November 17, 2008

Respectfully submitted,

By _____

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